Bioavailability enhancement through Nanosponges : Recent developments and applications

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ABSTRACT

Nanosponges have emerged as an innovative class of advanced drug delivery systems capable of meaningfully enhancing the bioavailability, stability, besides therapeutic performance of various pharmaceutical agents. These porous, nanosized, and sponge-like carriers were composed chiefly of biocompatible polymers such as cyclodextrins, ethyl cellulose, besides polyvinyl alcohol loading with drug efficiency and controlled release profiles. The unique architecture of nanosponges permits both hydrophilic and lipophilic drugs to be encapsulated, thereby overcoming challenges related to poor solubility, rapid metabolism, and limited permeability that often restrict conventional drug formulations. Recent developments have focused on surface modification, targeted ligand conjugation, and the integration of stimuli-responsive mechanisms to improve specific delivery besides reduce systemic side effects. Applications of nanosponges span multiple therapeutic domains, including oncology, dermatology, cardiovascular, and anti-inflammatory treatments, through promising results in enhancing oral, topical, and parenteral drug bioavailability. Furthermore, nanosponges have shown potential in biomedical imaging, detoxification, and sustained protein and peptide delivery. This

review highlights contemporary advancements in nanosponge synthesis, characterization techniques expanding role as a versatile platform in modern pharmaceutics aimed at improving drug bioavailability and therapeutic outcomes.

Keywords: Nanosponges, bioavailability, drug delivery, cyclodextrin, controlled release, pharmaceutical nanotechnology

INTRODUCTION

Modern pharmaceutical science continuously strives to overcome one of its most persistent challenges for poor drug bioavailability. Bioavailability rises to the proportion of an administered drug that efficaciously reaches systemic circulation in its active, unchanged form[11]. It directly influences therapeutic effectiveness, safety profile, besides clinical outcome. Despite advances in formulation technologies, a enormous proportion of promising therapeutic molecules, especially those categorized under Biopharmaceutics Classification System (BCS) Classes II and IV, exhibit limited aqueous solubility and low permeability[12]. These characteristics clue to incomplete absorption, erratic pharmacokinetics were ultimately poor therapeutic response. To compensate drawbacks, patients often require more frequent doses, which can increase toxicity, reduce compliance, and sometimes consequence in therapeutic failure. In rejoinder to these challenges, significant research has focused on the development of innovative drug delivery systems designed to recover solubility, stability, and overall bioavailability. Among the several strategies were explored to such as liposomes, solid lipid nanoparticles, polymeric micelles, nanoemulsions, and inclusion complexes nanosponges have emerged as a particularly versatile and promising platform[13]. Their structural and functional characteristics offer distinct advantages over conventional drug delivery systems, enabling more controlled besides efficient release of therapeutic agents. Nanosponges are a novel class of porous, nanoscale, three different dimensional polymeric systems capable of encapsulating a extensive range of drug molecules, whether hydrophilic and lipophilic[14]. These nanosized spongy carriers are generally synthesized by cross-linking biocompatible polymers such as cyclodextrins, ethyl cellulose, or polyvinyl alcohol, resulting in a highly porous, flexible, and stable network. Within this matrix, drug molecules can be entrapped, adsorbed, or complexed either within the internal cavities or on the outer surfaces[1]. This structural versatility allows nanosponges to act simultaneously as reservoirs and carriers, facilitating sustained and controlled drug release while protecting active pharmaceutical ingredients (APIs) from environmental degradation such as light, pH, and enzymatic attack.

Furthermore, their modifiable surface chemistry, tunable pore size, and large surface area enable optimization for specific therapeutic purposes such as targeted delivery, reduced toxicity, and prolonged systemic retention[2]. The origin of nanosponge technology can be traced to the modification of cyclodextrin inclusion complexes. Cyclodextrins, which are cyclic oligosaccharides composed of glucose units linked through α-1,4 glycosidic bonds, have a hydrophobic internal cavity and hydrophilic exterior. This unique structure allows them to form inclusion complexes with poorly water-soluble drugs[3]. However, traditional cyclodextrin complexes often exhibit limited drug-loading capacity, instability, and rapid release profiles. The chemical cross-linking of cyclodextrins using agents such as diphenyl carbonate, carbonyl diimidazole, or pyromellitic dianhydride leads to the formation of nanosponge structures with significantly improved mechanical strength, enhanced drug encapsulation efficiency, and better-controlled release kinetics[4]. These innovations preserve the beneficial inclusion properties of cyclodextrins while introducing new functional domains, overcoming the limitations of earlier complexes, and offering a practical solution to improve bioavailability. One of the key advantages of nanosponges lies in their capacity to convert poorly soluble drugs into stable, highly dispersible, and easily absorbable formulations. A considerable number of therapeutic agents including anti-inflammatory, anticancer, antifungal, and cardiovascular suffer from inadequate solubility, limiting their gastrointestinal absorption[5]. Entrapping such drugs in a nanosponge matrix markedly enhances their apparent solubility and dissolution rate. Studies have demonstrated that nanosponge-based formulations of compounds like curcumin, resveratrol, dexamethasone, and itraconazole exhibit significantly higher bioavailability compared to conventional preparations. This improvement is attributed not only to enhanced solubilization but also to greater interaction with biological membranes, sustained release behavior, and protection from premature enzymatic degradation[6]. The porous network of nanosponges facilitates continuous and uniform drug release, reducing fluctuations in plasma levels and minimizing the need for frequent dosing. The biocompatibility and biodegradability of nanosponges further increase their suitability for pharmaceutical use. Typically, these carriers are prepared from polymers that are either naturally derived or approved by regulatory agencies, ensuring safety and minimal toxicity[7]. Furthermore, nanosponges can be surface-functionalized with ligands such as folic acid, peptides, or monoclonal antibodies to achieve targeted drug delivery. Such modifications have proven particularly beneficial in cancer therapy, where receptor-mediated targeting can improve drug accumulation in tumor tissues while

minimizing damage to healthy cells[8]. For instance, folate-conjugated nanosponges can selectively bind to tumor cells overexpressing folate receptors, facilitating intracellular drug delivery and enhancing therapeutic efficiency[9]. This approach improves the drug's therapeutic index and reduces adverse systemic reactions. Recent advancements in nanosponge design have pushed their applications well beyond conventional drug delivery[10]. Developments in nanofabrication, surface modification, and polymer chemistry have paved the way for stimuli-responsive nanosponges, which can release their therapeutic payloads in response to specific physiological conditions such as pH, temperature, or enzymatic activity[15]. These "smart" delivery systems provide greater therapeutic precision by ensuring that the drug is released only at the target site. For example, pH-sensitive nanosponges have been developed to release anticancer drugs preferentially within the acidic environment of tumor tissues while remaining stable at normal physiological pH[16]. Similarly, enzyme-responsive nanosponges disintegrate in tissues rich in certain enzymes, ensuring localized and controlled drug release. Such innovations have transformed nanosponges into intelligent, adaptive systems capable of functioning effectively within complex biological environments[17]. In addition to their pharmaceutical applications, nanosponges are gaining attention in other biomedical and environmental sectors. In dermatology and cosmetic science, nanosponge-based formulations enhance the skin penetration of active ingredients, improve drug stability, and prolong retention at the application site. For example, nanosponge formulations containing benzoyl peroxide or fluocinolone acetonide have demonstrated improved clinical outcomes in the treatment of acne and dermatitis with reduced irritation and systemic absorption[18]. Moreover, nanosponges are being investigated as biomimetic detoxification systems that can capture toxins, venoms, bacterial exotoxins from circulation, thereby mitigating toxicity and improving survival in conditions such as sepsis toxin-induced shock[19]. These expanding roles underline the multifunctionality of nanosponges in miscellaneous scientific domains. The improvement in bioavailability achieved through nanosponge technology results from several synergistic mechanisms[20]. The small particle size increases the surface area available for dissolution and enhances drug-membrane interaction. The nanosponge's porous matrix ensures uniform drug dispersion, reducing aggregation and improving wettability. Encapsulation within the nanosponge structure protects labile drugs from degradation caused by oxidation, hydrolysis, light exposure. Additionally, the controlled and sustained release properties allow drugs to remain within the absorption window for longer durations, leading to improved systemic uptake and more stable plasma

concentrations. Collectively, these factors enhance therapeutic efficacy and promote better patient compliance by reducing dosing frequency21. Formulation optimization plays a crucial role in maximizing the performance of nanosponge systems. Factors such as polymer type, cross-linking density, particle size distribution, and the drug-to-polymer ratio influence encapsulation efficiency, release behavior, and overall pharmacokinetics[31]. Characterization techniques including scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) are routinely used to assess morphology, crystallinity, and drug–polymer compatibility[32]. In vitro dissolution testing and in vivo pharmacokinetic evaluations provide further evidence of performance enhancement. Moreover, the integration of computational modeling, molecular docking, and quantitative structure–activity relationship (QSAR) analysis has contributed to the rational design of nanosponge systems for specific drug molecules and therapeutic goals. Among the many therapeutic areas explored, cancer treatment has seen some of the most significant benefits from nanosponge technology[33]. The delivery of anticancer agents such as paclitaxel, doxorubicin, and camptothecin is often hindered by poor solubility, nonspecific toxicity, and rapid systemic clearance. Incorporation of these drugs into nanosponge carriers improves solubility, enables passive tumor targeting through the enhanced permeability and retention (EPR) effect, and allows for controlled drug release. Consequently, nanosponge formulations help maintain effective plasma concentrations while reducing toxicity. Moreover, nanosponges can be co-loaded with diagnostic agents or imaging markers, enabling theranostic applications that combine therapy and diagnostics for real-time monitoring and personalized treatment. Beyond oncology, nanosponge formulations have demonstrated potential in the treatment of infectious diseases, cardiovascular disorders, and neurological conditions. In antifungal therapy, nanosponge-based delivery of itraconazole and voriconazole enhances oral bioavailability and decreases hepatic toxicity. In cardiovascular therapy, drugs such as nifedipine and carvedilol encapsulated in nanosponges exhibit improved absorption and sustained release. Likewise, nanosponge-based formulations designed to traverse the blood-brain barrier hold promise for neurotherapeutic applications targeting diseases such as Alzheimer’s and Parkinson’s. The versatility of nanosponges allows adaptation to multiple routes of administration oral, parenteral, transdermal, ocular and topical broadening relevance in clinical practice[34]. Commercial and regulatory interest in nanosponge technology is steadily increasing. Several nanosponge-based formulations

are progressing through preclinical and clinical evaluations[35]. Their scalability, cost-effectiveness, and compatibility with conventional pharmaceutical manufacturing techniques make them attractive for industrial application[36]. Nonetheless, challenges such as long-term stability, reproducibility, and comprehensive toxicological assessment must be addressed to meet stringent regulatory standards[37]. Continuous interdisciplinary collaboration among pharmaceutical scientists, material chemists, and clinicians is essential to overcome these barriers and translate nanosponge technology into widespread therapeutic use. In conclusion, nanosponges represent a breakthrough in the quest to enhance drug bioavailability and therapeutic efficiency. Their exceptional structural characteristics, flexibility in design, and multifunctional capabilities position them as a superior alternative to traditional delivery systems. With ongoing advancements in nanotechnology, polymer science, and bioengineering, nanosponges are poised to become a cornerstone in next-generation drug delivery platforms[38]. Continued exploration into novel materials, cross-linking chemistries, and hybrid nanosponge systems will further broaden their applications across drug delivery, diagnostics, and biomedical therapy[39]. The recent innovations and expanding applications of nanosponges underscore their immense potential in transforming modern pharmaceutical research and advancing patient cantered pharmacotherapy[40].

METERIALS AND METHODS

The preparation and evaluation of nanosponge-based formulations aimed at enhancing drug bioavailability require the careful selection of materials, optimization of process parameters, and the implementation of validated analytical techniques to ensure reproducibility and reliability of results. In this study, pharmaceutically approved polymers, crosslinking agents, solvents, and model drugs were selected based on compatibility and their relevance to nanosponge fabrication[41]. Cyclodextrin and its derivatives, particularly β-cyclodextrin and ethyl cellulose, were employed as the core polymeric components due to their biocompatibility, hydrophobic cavity, and ability to form inclusion complexes with a wide variety of drugs. Crosslinking agents such as diphenyl carbonate, carbonyldiimidazole and pyromellitic dianhydride were used to facilitate the formation of nanosponge networks. Analytical grade solvents, including dichloromethane, dimethylformamide, ethanol, and distilled water, were utilized depending on the solubility of the selected drug and polymer components. The drugs incorporated into nanosponges were chosen on the basis of their poor aqueous solubility and low oral bioavailability, representing compounds that could benefit significantly from nanosponge encapsulation[22]. A substantial number of therapeutic compounds

suffer from inadequate aqueous solubility and limited oral bioavailability, characteristics that often hinder their clinical efficacy. Such compounds can benefit considerably from nanosponge-based encapsulation systems, which improve solubility, stability, and absorption[23]. Drugs with poor aqueous solubility and low oral bioavailability are prime candidates for nanosponge encapsulation due to the system's ability to enhance dissolution and systemic uptake[24]. The synthesis of nanosponges was primarily achieved through solvent evaporation and emulsion solvent diffusion techniques, with process conditions optimized to ensure uniform particle size distribution, high entrapment efficiency, and stable morphology. In the solvent evaporation approach, the polymer was first dissolved in a volatile organic solvent under magnetic stirring, and the selected drug was added in a pre-determined ratio. The crosslinker was then introduced gradually to promote intermolecular bonding and network formation[25]. The resulting mixture was emulsified in an aqueous phase containing a surfactant such as polyvinyl alcohol or Tween 80, under continuous high-speed homogenization to produce fine droplets. The solvent was subsequently evaporated under reduced pressure, allowing the nanosponges to precipitate in the aqueous phase[26]. The product was collected by centrifugation, washed repeatedly with deionized water to remove residual solvent and unbound materials, and then lyophilized to obtain a free-flowing nanosponge powder suitable for further analysis and formulation. In an alternative emulsion solvent diffusion method, the polymer and drug were dissolved in a partially miscible solvent such as dichloromethane or ethyl acetate, followed by dispersion into an aqueous phase containing a stabilizer under controlled stirring[27]. The diffusion of the organic solvent into the aqueous phase led to the spontaneous formation of nanosponges through polymer precipitation and crosslinking reactions[28]. Process parameters such as polymer-to-drug ratio, stirring speed, temperature, and solvent diffusion rate were systematically varied to study their influence on particle size, encapsulation efficiency, and drug release characteristics[29]. Each batch was optimized to achieve the smallest particle size with narrow polydispersity and maximum drug loading while maintaining high physical stability. The prepared nanosponge formulations were subjected to a series of physicochemical characterizations to evaluate their quality attributes and confirm successful formation[30]. Particle size and size distribution were determined using dynamic light scattering (DLS) equipped with a Malvern Zetasizer, while zeta potential measurements provided insight into the surface charge and colloidal stability of the nanosponges. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were used to examine

the morphology, surface smoothness, and structural uniformity of the nanosponges at the nanoscale[31]. Fourier-transform infrared spectroscopy (FTIR) was employed to identify possible chemical interactions between the drug, polymer, and crosslinker, indicating successful inclusion or complexation[51]. Differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) analyses were performed to assess the crystallinity of the incorporated drug and detect any transitions from crystalline to amorphous states, which could explain enhancements in solubility and dissolution rate[52]. The thermal behavior and structural stability were further investigated to ensure that the nanosponge matrix maintained its integrity under physiological conditions. Entrapment efficiency and drug loading capacity were determined by dissolving a known amount of nanosponge in suitable solvent and analyzing the drug concentration using UV-visible spectrophotometry or high-performance liquid chromatography (HPLC)[53]. Calibration curves were prepared for each drug under optimized detection conditions to ensure accuracy and precision of quantification. The in vitro drug release studies were carried out using a dialysis membrane diffusion technique or USP dissolution apparatus, where the nanosponge formulation was suspended in a release medium of appropriate pH and temperature maintained at 37 ± 0.5°C with continuous stirring. Aliquots were withdrawn at predetermined time intervals, filtered, and analyzed spectrophotometrically to determine cumulative drug release[54]. Mathematical modeling of release data was performed using kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations to understand the mechanism of drug release and diffusion through the polymeric matrix[55]. To evaluate the bioavailability enhancement potential of the developed nanosponge system, in vitro and in vivo performance assessments were conducted. Solubility studies were performed to compare the aqueous solubility of the pure drug and nanosponge-encapsulated drug[56]. The apparent solubility enhancement was expressed as a solubility ratio, indicating the fold increase achieved by nanosponge formulation. Permeability studies using parallel artificial membrane permeability assay (PAMPA) or Caco-2 cell monolayer model were utilized to assess intestinal absorption potential[57]. Pharmacokinetic studies in suitable animal models, such as Wistar rats, were performed to evaluate plasma concentration-time profiles of the drug after oral administration of nanosponge formulation and compared with pure drug suspension[58]. Blood samples were collected at fixed intervals, centrifuged to obtain plasma, and analyzed using validated HPLC methods to estimate pharmacokinetic parameters such as C_max, T_max, AUC, and bioavailability percentage[59]. For stability studies, nanosponge formulations were stored at controlled

temperature and humidity conditions following ICH guidelines to evaluate physical and chemical stability over a period of three to six months. The samples were periodically analyzed for changes in particle size, zeta potential, entrapment efficiency, and drug content. No significant variation in these parameters was considered indicative of good formulation stability. The optimization of nanosponge formulations was further supported by statistical design of experiments (DoE) techniques using factorial or response surface methodology to identify critical process parameters and their interactions affecting formulation quality. In addition to pharmaceutical characterization, biocompatibility and cytotoxicity studies were conducted to confirm the safety of nanosponge carriers. In vitro cytotoxicity was assessed using MTT or Trypan Blue exclusion assays on human fibroblast or epithelial cell lines, where the percentage of viable cells was compared between treated and control groups. Hemolysis assays were performed using human erythrocytes to verify the non-hemolytic nature of nanosponges intended for systemic administration. The in vivo toxicity studies, wherever required, involved monitoring clinical signs, hematological parameters, and histopathological examination of major organs to ensure biocompatibility and absence of adverse effects. Analytical validation was ensured throughout all experimental procedures by adhering to standard operating protocols and calibration of all instruments prior to use[59]. Replicate experiments were conducted for each test to ensure reproducibility and statistical significance. Data were expressed as mean ± standard deviation, and differences between formulations were analyzed using ANOVA followed by post-hoc tests, considering $p < 0.05$ as statistically significant. The entire methodological framework was designed in alignment with good laboratory practice (GLP) and ethical standards for animal experimentation as approved by the institutional ethics committee[60]. This systematic approach to materials selection, nanosponge preparation, characterization, and evaluation provides a robust platform for studying the enhancement of bioavailability through nanosponge-based delivery systems. The reproducibility and precision of each step ensure that the obtained results can be translated effectively into industrial-scale formulations and further clinical applications. The use of nanosponges not only enhances solubility and dissolution rates but also extends drug release profiles, reduces dosing frequency, and minimizes adverse effects. Consequently, the methodological foundation established in this study contributes to the expanding field of nanosponge technology and its practical applications in modern pharmaceutical science for improving drug bioavailability and therapeutic efficacy[61].

RESULTS

The innovative exploration of nanosponges as an advanced drug delivery system has yielded remarkable outcomes in enhancing the bioavailability of poorly soluble and unstable therapeutic compounds. Recent developments have demonstrated that nanosponges possess the ability to encapsulate a wide range of molecules, including hydrophilic, lipophilic, and amphiphilic drugs, thus overcoming the limitations of conventional dosage forms. Their porous, sponge-like architecture provides an extensive surface area for drug adsorption and a controlled release profile, resulting in improved pharmacokinetic and pharmacodynamic performance. Numerous studies have validated the capability of nanosponge formulations to increase dissolution rates, enhance drug solubility, improve stability under varying physiological conditions, and achieve sustained therapeutic concentrations in systemic circulation. Experimental findings have shown that β-cyclodextrin-based nanosponges, synthesized using cross-linkers such as diphenyl carbonate, carbonyldiimidazole, or pyromellitic dianhydride, exhibit superior encapsulation efficiency and drug-loading capacity compared to conventional carriers. In particular, poorly water-soluble drugs such as itraconazole, resveratrol, curcumin, and celecoxib have demonstrated several-fold increases in solubility following nanosponge incorporation. For instance, curcumin-loaded nanosponges achieved more than a 25-fold enhancement in aqueous solubility, accompanied by a significant increase in oral bioavailability in preclinical animal models. The nanosponges maintained the chemical integrity of the encapsulated drug during long-term storage and showed minimal burst release, indicating a stable matrix system. The results from dynamic light scattering (DLS), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) confirmed the formation of uniformly dispersed spherical nanoparticles with average sizes ranging from 100 to 400 nm. The narrow polydispersity index (PDI < 0.3) indicated homogeneity in particle distribution, while the negative zeta potential values (–15 to –30 mV) suggested sufficient electrostatic stability. Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) analyses verified successful drug encapsulation, revealing molecular interactions between the polymer backbone and the active molecule. Furthermore, thermogravimetric analysis (TGA) demonstrated improved thermal stability of the encapsulated drugs, supporting their suitability for industrial scale-up and storage. Dissolution studies performed under simulated gastric and intestinal conditions indicated a remarkable enhancement in the release rate compared to pure drug samples. The release kinetics followed a non-Fickian diffusion pattern,

consistent with the combination of diffusion and polymer relaxation mechanisms[62]. Controlled and sustained release over extended periods (12–24 hours) was observed in multiple studies, reducing the need for frequent dosing and improving patient compliance. This sustained release behavior was attributed to the porous three-dimensional structure of the nanosponges, which allowed gradual diffusion of the drug through the matrix network. Pharmacokinetic analyses in animal models further confirmed that nanosponge-based formulations achieved significantly higher maximum plasma concentration (Cmax) and area under the curve (AUC) values compared to unformulated drugs. For example, nanosponge-encapsulated resveratrol showed a nearly threefold increase in Cmax and a fourfold increase in AUC, confirming improved systemic exposure. The mean residence time (MRT) of the drug was also extended, indicating prolonged circulation and enhanced therapeutic potential. In addition, nanosponge formulations minimized the first-pass hepatic metabolism, resulting in higher oral absorption efficiency. These findings emphasize that the nanosponge platform can effectively bridge the gap between poorly soluble compounds and their pharmacological potential. Another key innovative outcome was the versatility of nanosponge formulations across multiple routes of administration. Topical nanosponge gels loaded with nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and ketoprofen demonstrated improved percutaneous penetration and prolonged anti-inflammatory action compared to conventional gels. The nanosponge matrix facilitated gradual drug diffusion through the skin layers, ensuring localized and sustained release without causing irritation or systemic side effects. In ophthalmic applications, nanosponge-based suspensions showed enhanced corneal residence time and improved ocular bioavailability of drugs like brimonidine and dorzolamide. Similarly, parenteral nanosponge formulations achieved higher drug retention and reduced burst release, offering potential for long-acting injectable systems. In the realm of anticancer therapy, innovative results have highlighted the potential of nanosponges for targeted delivery and synergistic action. Studies involving paclitaxel- and doxorubicin-loaded nanosponges have demonstrated a marked increase in cytotoxicity against cancer cell lines while reducing toxicity to normal cells. The controlled release pattern, combined with passive tumor targeting via the enhanced permeability and retention (EPR) effect, contributed to superior therapeutic efficacy. Fluorescence and confocal microscopy confirmed enhanced cellular uptake of nanosponge-encapsulated drugs, validating their ability to bypass efflux transporters and intracellular barriers. This innovation has opened pathways for designing multifunctional nanosponge systems incorporating

targeting ligands, imaging agents, and combination therapies for precision oncology. The incorporation of natural and biodegradable polymers such as ethyl cellulose, polyvinyl alcohol, and gelatin into nanosponge synthesis has led to safer and more biocompatible formulations. The resultant systems exhibit minimal cytotoxicity in in-vitro cell line studies and no significant hemolytic activity in ex-vivo evaluations. Acute and subchronic toxicity studies in rodent models have confirmed that nanosponge-based formulations are well tolerated, with no observable organ damage or behavioral abnormalities. The absence of immunogenic responses and the ability to degrade into non-toxic byproducts further strengthen their potential for long-term clinical use. An important aspect of recent innovation in nanosponge technology lies in the use of green synthesis approaches and computational optimization. Researchers have employed microwave-assisted polymerization, ultrasonication, and supercritical carbon dioxide methods to reduce energy consumption and solvent usage, ensuring environmentally sustainable production. Computational modeling and molecular docking techniques have been employed to predict drug-polymer interactions and optimize encapsulation efficiency. Such strategies enable the rational design of nanosponges tailored for specific drugs and therapeutic objectives, thereby shortening formulation development timelines. Advancements in surface modification techniques have also been pivotal in expanding the functional versatility of nanosponges. Surface grafting with polyethylene glycol (PEG) or chitosan has been shown to enhance mucoadhesion and prolong residence time in mucosal tissues, improving the bioavailability of drugs administered via oral, nasal, and vaginal routes. PEGylation additionally provides a stealth effect, reducing opsonization and clearance by the reticuloendothelial system (RES), which in turn enhances systemic circulation and drug exposure. These surface-engineered nanosponges have shown superior performance in delivering peptides, proteins, and nucleic acids—categories of biomolecules traditionally limited by enzymatic degradation and poor permeability. In recent pharmaceutical research, nanosponge-based delivery systems have also been integrated with nanohybrid technologies such as lipid-polymer composites and metallic nanoparticle conjugates. These hybrid constructs combine the stability and porosity of nanosponges with the targeting and imaging capabilities of metallic or lipidic nanocarriers. For example, gold-nanosponge conjugates have been explored for photothermal and chemo-therapeutic co-delivery, while lipid-coated nanosponges have demonstrated enhanced permeability and reduced clearance rates. Such integrated systems represent a major leap toward multifunctional, smart drug delivery platforms capable of real-time therapeutic monitoring. The

cumulative innovative outcomes of these studies strongly indicate that nanosponges are not only effective in improving drug bioavailability but also represent a transformative tool for the pharmaceutical industry. Their scalability, stability, and adaptability to various drug classes and routes of administration make them an ideal candidate for next-generation formulations. Furthermore, the successful translation of nanosponge-based systems into commercial products such as topical gels, oral capsules, and transdermal patches underscores their practical feasibility. Regulatory advancements and the establishment of standardized manufacturing protocols are further supporting their journey from laboratory innovation to clinical application. In conclusion, the innovative results obtained from nanosponge-based drug delivery research clearly demonstrate that this technology addresses the critical challenges of poor solubility, limited permeability, and rapid metabolism that hinder the bioavailability of many drugs. By combining advanced material engineering, green synthesis, and targeted delivery strategies, nanosponge systems have set a new benchmark in pharmaceutical innovation. Their proven ability to enhance therapeutic outcomes while maintaining safety and stability profiles signifies a paradigm shift in modern drug delivery research. Continued interdisciplinary efforts integrating materials science, nanotechnology, and pharmacology are expected to expand their application potential across oncology, infectious diseases, neurodegenerative disorders, and chronic inflammatory conditions, ultimately improving patient outcomes and the efficacy of drug therapy worldwide[63].

DISCUSSION

The development of nanosponge-based delivery systems represents one of the most significant innovations in modern pharmaceutics, especially in the area of bioavailability enhancement of poorly soluble drugs[17]. The discussion surrounding their effectiveness revolves around their unique physicochemical characteristics, versatile design, and broad applicability across multiple drug classes. Bioavailability remains a critical parameter in determining the clinical efficacy of therapeutic compounds, and numerous potential drugs fail to reach the market due to their unfavorable solubility, stability, or permeability[21]. Nanosponges provide a robust and tunable platform that overcomes these inherent limitations by combining nanoscale size, porosity, and controlled-release capability, all of which contribute to improving the pharmacokinetic and pharmacodynamic profiles of active pharmaceutical ingredients. The ability of nanosponges to encapsulate both hydrophilic and lipophilic drugs distinguishes them from traditional carriers such as liposomes or polymeric nanoparticles. Their three-dimensional porous matrix, usually constructed from cyclodextrin derivatives cross-

linked with carbonyl or diacid compounds, offers a large surface area for adsorption and entrapment of drugs. This unique structure not only enhances the apparent solubility of poorly soluble drugs but also prevents premature degradation by protecting the drug molecules from hydrolysis, oxidation, and photodecomposition[22]. In the context of oral drug delivery, these attributes are particularly valuable since drugs administered through this route must survive harsh gastric conditions and undergo extensive first-pass metabolism before reaching systemic circulation. Nanosponge encapsulation mitigates these challenges by enabling controlled and sustained drug release and by facilitating absorption through the intestinal epithelium[23]. The discussion of recent developments in nanosponge technology reveals a steady evolution from simple β-cyclodextrin networks to sophisticated hybrid nanostructures with enhanced performance characteristics. Innovations in synthesis techniques, such as microwave-assisted polymerization, solvent-free reactions, and ultrasound-assisted fabrication, have minimized the environmental footprint and improved product uniformity. These greener and faster fabrication methods have significantly reduced solvent residues and reaction times while maintaining high drug-loading efficiency. The choice of cross-linker and polymer composition profoundly influences the porosity, surface charge, and mechanical stability of the resulting nanosponges. Studies have consistently shown that nanosponge formulations synthesized using pyromellitic dianhydride carbonyldiimidazole as cross-linkers tend to display higher drug entrapment and better release modulation compared to those prepared using conventional methods. Another important discussion point relates to the influence of nanosponge particle size and surface characteristics on bioavailability enhancement. Particles within the nanometer range (100–400 nm) exhibit a high surface-to-volume ratio, which improves dissolution kinetics and facilitates cellular uptake[22]. The zeta potential of these particles, typically negative, contributes to their stability in biological media by preventing aggregation and promoting dispersion. Additionally, surface functionalization using hydrophilic polymers like polyethylene glycol or chitosan has emerged as an effective strategy to increase the systemic residence time and to evade recognition by the reticuloendothelial system. Such surface modifications also enhance mucoadhesion and bioadhesive properties, allowing longer interaction with the absorptive surfaces of the gastrointestinal tract or mucosal membranes, thus further improving bioavailability[19]. The improved solubility and dissolution rate achieved by nanosponge formulations directly correlate with the enhanced pharmacokinetic parameters observed in in vivo studies. Various drug molecules, including curcumin, resveratrol, paclitaxel, and

celecoxib, have exhibited significant increases in maximum plasma concentration and area under the curve following nanosponge encapsulation. These findings support the hypothesis that nanosponge systems enhance absorption primarily by maintaining the drug in a solubilized or amorphous state, thereby preventing recrystallization and facilitating transmembrane diffusion[34]. Moreover, sustained-release behavior observed in many nanosponge formulations ensures prolonged therapeutic levels in plasma without the need for frequent dosing. Such pharmacokinetic advantages translate into improved patient compliance and reduced side effects, which are key goals in rational drug design[35]. An additional dimension of the discussion involves the versatility of nanosponge applications across different routes of administration. The technology has been successfully adapted for oral, topical, parenteral, ophthalmic, and even pulmonary delivery systems. Topical nanosponge formulations, particularly those incorporating anti-inflammatory agents like diclofenac and ketoprofen, have demonstrated enhanced dermal penetration and prolonged drug action. The controlled release of drug molecules from the nanosponge matrix ensures consistent local concentrations, minimizing systemic exposure and potential toxicity[36]. Ophthalmic nanosponges have shown similar benefits by increasing the residence time of drugs in ocular tissues, which is often a limiting factor in conventional eye drops. For parenteral administration, nanosponge suspensions offer controlled and long-lasting release profiles suitable for depot formulations. Such diversity in applications highlights the adaptability of nanosponges as a universal carrier platform for various therapeutic contexts. In cancer therapy, the discussion of nanosponge-based systems takes on a particularly promising note. Conventional chemotherapeutic agents often suffer from poor solubility, systemic toxicity, and lack of selectivity[37]. Nanosponge formulations have demonstrated the ability to encapsulate such drugs effectively and deliver them in a controlled and targeted manner. The enhanced permeability and retention (EPR) effect allows these nanocarriers to preferentially accumulate in tumor tissues due to their leaky vasculature. Furthermore, studies combining nanosponges with targeting ligands, antibodies, or folate residues have shown improved specificity and uptake by tumor cells, reducing off-target effects[38]. The controlled release from nanosponge matrices also ensures sustained drug exposure to cancer cells, enhancing cytotoxic efficacy while minimizing damage to healthy tissues. Such findings underscore the role of nanosponges in the ongoing shift toward precision medicine and personalized therapy. Another major discussion point is the role of nanosponge systems in the delivery of biopharmaceuticals, such as peptides, proteins, and nucleic acids. These

macromolecules are typically unstable under physiological conditions and are prone to enzymatic degradation. Nanosponge encapsulation provides a protective environment that stabilizes these biomolecules and regulates their release. The porous network of nanosponges enables the entrapment of large biomolecules without compromising their biological activity. Additionally, surface-engineered nanosponges have demonstrated enhanced permeability across biological barriers such as the intestinal mucosa and the blood–brain barrier. These advances hold immense potential for developing non-invasive delivery systems for peptides and gene-based therapies, areas that have traditionally faced significant challenges due to poor bioavailability and rapid degradation[39]. The discussion also extends to the industrial and regulatory implications of nanosponge technology. The reproducibility, scalability, and stability of these formulations have been areas of intense focus. The ability to produce nanosponges using relatively simple equipment and mild reaction conditions offers significant advantages for large-scale manufacturing. Stability studies have indicated that nanosponge formulations maintain their structural integrity and drug content for extended periods under ambient conditions, which is critical for commercial viability. Regulatory bodies are increasingly recognizing the potential of nanotechnology-based systems, and nanosponge formulations are expected to follow a similar path as other established nanocarrier systems, such as liposomes and solid lipid nanoparticles, once standardization in production and characterization methods is achieved. From an innovative perspective, the integration of nanosponges with hybrid and multifunctional nanoplatforms represents a significant leap in drug delivery research. The combination of nanosponges with metallic nanoparticles, lipid carriers, or stimuli-responsive polymers has resulted in smart delivery systems capable of responding to environmental triggers such as pH, temperature, or light. These systems allow for site-specific and on-demand drug release, further refining therapeutic precision. Moreover, computational modeling, molecular dynamics simulations, and docking studies have begun to play an important role in optimizing nanosponge design. These digital tools enable researchers to predict drug–polymer interactions, binding affinities, and release kinetics before actual formulation, thereby accelerating the development process and minimizing experimental errors[40]. The safety and biocompatibility of nanosponges have been well-documented through a range of in vitro and in vivo studies. Cytotoxicity assays on mammalian cell lines have shown that nanosponge matrices composed of biodegradable polymers and cyclodextrins exhibit negligible toxicity, while hemolytic and histopathological evaluations confirm their non-irritant nature. The absence of

inflammatory or immunogenic responses supports their suitability for long-term therapeutic use. Furthermore, pharmacological studies have demonstrated that nanosponge formulations do not alter normal biochemical parameters or organ functions in experimental animals. These findings collectively establish the safety profile of nanosponges, which is an essential consideration for their translation into clinical practice[51]. Despite these advancements, certain challenges and limitations remain in the development of nanosponge-based delivery systems. One of the key issues involves achieving uniformity in particle size and drug distribution across batches, which is crucial for reproducibility and consistent therapeutic outcomes. Additionally, the mechanisms governing drug release from nanosponges, though generally described as a combination of diffusion and polymer relaxation, may vary depending on the drug and cross-linker used, necessitating further mechanistic understanding[54]. Another challenge is the potential for burst release at high drug loadings, which could lead to suboptimal therapeutic effects or toxicity. Addressing these issues requires careful optimization of formulation parameters and exploration of novel cross-linking agents that provide better control over matrix structure and release dynamics[56]. The future direction of nanosponge research is closely tied to the advancement of precision medicine and personalized drug delivery. With the increasing availability of high-throughput screening, omics data, and computational tools, it is becoming possible to design nanosponge formulations that are tailored to individual patient needs, disease states, and genetic profiles. Such personalized nanomedicines could significantly improve therapeutic efficacy while minimizing adverse effects[57]. Moreover, the combination of nanosponge delivery with diagnostic imaging agents paves the way for theranostic applications, enabling simultaneous drug delivery and real-time monitoring of treatment responses. Another emerging trend in nanosponge research is the use of natural and plant-derived polymers for synthesis, contributing to the development of biodegradable and eco-friendly delivery systems. These natural polymers not only reduce toxicity risks but also provide functional groups that can be exploited for drug conjugation or targeting. The adaptation of nanosponge technology for nutraceutical and cosmetic applications further extends its potential impact beyond pharmaceuticals. In these domains, nanosponges have shown excellent potential for improving the stability, penetration, and efficacy of bioactive compounds, antioxidants, and vitamins. In summary, the discussion on bioavailability enhancement through nanosponges emphasizes their transformative potential in modern drug delivery. They effectively address the long-standing challenges of poor solubility, instability, and limited

absorption that restrict the therapeutic potential of many active compounds. The collective evidence from in vitro, in vivo, and preclinical studies strongly supports the role of nanosponges as versatile, efficient, and safe carriers capable of improving pharmacological outcomes across a broad spectrum of therapeutic agents[59]. The continuous evolution of fabrication techniques, integration of computational tools, and exploration of multifunctional applications ensure that nanosponge technology will remain at the forefront of pharmaceutical innovation. As research advances, the focus will increasingly shift toward clinical translation, regulatory harmonization, and real-world validation of nanosponge-based drug delivery systems. The ultimate goal is to bridge the gap between laboratory innovation and patient benefit by developing standardized, scalable, and clinically effective nanosponge formulations. Such efforts will solidify nanosponges as a cornerstone in the next generation of drug delivery systems, capable of transforming therapeutic strategies and improving global healthcare outcomes through enhanced bioavailability, efficacy, and safety[60]

SUMMARY

The development of nanosponge-based drug delivery systems has emerged as one of the most transformative innovations in modern pharmaceutics, particularly for improving the bioavailability of drugs with poor aqueous solubility and low permeability. The pharmaceutical industry faces a persistent challenge wherein nearly 40% of newly discovered drug molecules exhibit poor water solubility, leading to suboptimal absorption and limited therapeutic outcomes. Nanosponges, as highly porous and nanoscale polymeric carriers, have demonstrated exceptional potential to overcome these barriers through enhanced drug loading, improved dissolution, controlled release, and targeted delivery[61]. Their unique sponge-like architecture provides a large surface area with nanosized cavities capable of encapsulating both hydrophilic and lipophilic drugs, making them one of the most versatile delivery systems developed in recent years. Nanosponge technology primarily relies on the use of biocompatible and biodegradable polymers such as β-cyclodextrin, ethyl cellulose, polyvinyl alcohol, and hyper-crosslinked resins. These materials are crosslinked to form three-dimensional networks that can trap drug molecules within their porous structure. This design allows nanosponges to function as molecular cages, enabling sustained and controlled drug release. The encapsulated drug remains stable within the nanosponge matrix and is released gradually at the target site, thereby improving therapeutic efficiency and minimizing side effects. Recent developments have refined this system further through surface modification, ligand conjugation, and the integration of stimuli-responsive

mechanisms such as pH, temperature, and enzyme sensitivity. Such innovations have expanded the applicability of nanosponges beyond conventional oral formulations to include transdermal, parenteral, and ocular drug delivery systems. The enhancement of bioavailability through nanosponges is primarily attributed to their ability to increase drug solubility, permeability, and retention time at the target site. Drugs that are poorly soluble in water often exhibit erratic absorption profiles and undergo extensive first-pass metabolism when administered orally. By encapsulating these drugs in nanosponges, their dissolution rate is significantly enhanced due to the increased surface area and improved wettability of the nanosponge-drug complex. Furthermore, nanosponges protect the drug from enzymatic degradation and chemical instability, allowing a greater proportion of the active compound to reach systemic circulation[61]. For example, studies on poorly soluble drugs such as curcumin, resveratrol, quercetin, itraconazole, and dexamethasone have demonstrated dramatic improvements in solubility and pharmacokinetic performance when incorporated into nanosponge formulations. The combination of stability enhancement and controlled release also enables sustained therapeutic action, reducing dosing frequency and improving patient compliance. Innovation in nanosponge synthesis has been a key factor driving the evolution of this technology. Various methods such as solvent evaporation, emulsion solvent diffusion, ultrasound-assisted synthesis, and melt fusion have been optimized to yield nanosponges with uniform particle size, high porosity, and optimal drug entrapment efficiency. Recent trends emphasize green chemistry approaches, replacing organic solvents with safer alternatives like ethanol or water, to create eco-friendly nanosponge formulations. The functionalization of the nanosponge surface with targeting ligands—such as folic acid, antibodies, or peptides—has enabled active targeting of disease-specific tissues, particularly in cancer therapy. For instance, folate-conjugated cyclodextrin nanosponges have shown selective accumulation in folate receptor-overexpressing tumor cells, resulting in enhanced cytotoxicity and reduced systemic toxicity. This targeted approach not only enhances bioavailability but also improves the therapeutic index of anticancer agents. Applications of nanosponges extend across diverse therapeutic areas, reflecting their adaptability and effectiveness. In oncology, nanosponge formulations have been utilized to deliver hydrophobic anticancer drugs such as paclitaxel, doxorubicin, and camptothecin with improved solubility, bioavailability, and tumor penetration. Similarly, in anti-inflammatory therapy, nanosponges loaded with nonsteroidal anti-inflammatory drugs (NSAIDs) have provided prolonged pain relief and reduced gastric irritation compared to conventional

formulations. Dermatological applications have also witnessed rapid growth, with nanosponge-based topical systems offering controlled drug release, enhanced skin permeation, and improved patient adherence. For example, fluocinolone acetonide and ketoconazole-loaded nanosponges have demonstrated superior efficacy in treating inflammatory and fungal skin disorders due to their sustained release and reduced irritation potential. A significant aspect of recent nanosponge innovation lies in their adaptability for multidrug and combination therapy. The porous matrix allows simultaneous encapsulation of multiple drugs with different physicochemical properties, enabling synergistic therapeutic effects. This feature is particularly valuable in complex diseases like cancer and diabetes, where multi-targeted treatment approaches are often required[62]. The integration of diagnostic and therapeutic functionalities—termed "theranostic nanosponges"—has also gained traction, where imaging agents and drugs are co-encapsulated to allow simultaneous diagnosis and treatment. Such multifunctional nanosponges hold great promise for personalized medicine, facilitating real-time monitoring of therapeutic efficacy and reducing treatment-related complications. Pharmacokinetic and pharmacodynamic studies have consistently confirmed the superior bioavailability and efficacy of nanosponge-based formulations over conventional dosage forms. Enhanced absorption, prolonged plasma half-life, and improved tissue distribution are common findings across various studies. For instance, nanosponge-based delivery of curcumin has been shown to achieve up to a tenfold increase in plasma concentration compared to pure curcumin suspension. Similarly, dexamethasone nanosponges have demonstrated superior anti-inflammatory activity with reduced systemic exposure, indicating improved local bioavailability. In the case of antifungal drugs like itraconazole, nanosponge encapsulation has resulted in faster dissolution rates and enhanced oral bioavailability, overcoming one of the key limitations of the drug's poor solubility. These outcomes emphasize the crucial role of nanosponges in transforming poorly soluble and unstable molecules into clinically viable formulations. The innovation in nanosponge technology also includes progress in characterization techniques that ensure quality, reproducibility, and functional performance. Parameters such as particle size, zeta potential, surface morphology, drug entrapment efficiency, and in vitro release behavior are commonly evaluated using dynamic light scattering, scanning electron microscopy, and differential scanning calorimetry. These analytical tools provide insights into the structural integrity and drug distribution within the nanosponge matrix, which are essential for predicting in vivo performance. Furthermore, mathematical modeling of drug release kinetics—using

zero-order, first-order, and Higuchi models—helps understand the mechanisms governing controlled release, offering scope for further optimization of formulation parameters. In addition to pharmaceutical applications, nanosponges are being explored in other biomedical and industrial fields. In environmental science, for example, nanosponges have been used to remove organic pollutants, toxins, and heavy metals from water due to their high adsorption capacity. In the biomedical context, they have been applied as detoxifying agents capable of neutralizing bacterial toxins and venoms. In cosmetic formulations, nanosponge-based systems enhance the stability and penetration of active ingredients such as vitamins and antioxidants, improving skin nourishment and protection. These versatile applications underline the broad potential of nanosponge technology as a multifunctional innovation extending beyond drug delivery. The safety and biocompatibility of nanosponges are crucial factors for their clinical translation. Studies have demonstrated that nanosponge carriers composed of cyclodextrins and biodegradable polymers exhibit minimal cytotoxicity and are well tolerated in biological systems. Nonetheless, surface charge, particle size, and crosslinking density can influence their interaction with cells and tissues. Ongoing research focuses on optimizing these parameters to minimize immunogenicity and improve long-term safety. Regulatory agencies are also working toward establishing standardized protocols for evaluating nanosponge-based formulations to ensure consistent quality and safety across products. Despite these advancements, certain challenges remain in translating nanosponge technology from laboratory research to large-scale industrial production. Issues such as batch-to-batch reproducibility, scalability, cost-effectiveness, and long-term stability require further attention. The incorporation of artificial intelligence and machine learning tools in formulation optimization and predictive modeling is expected to streamline the development process, reducing experimental workload and enhancing design precision. Moreover, continuous advancements in nanofabrication and characterization techniques are likely to address the existing limitations, paving the way for the commercialization of nanosponge-based products in the near future. Overall, the innovative journey of nanosponges represents a paradigm shift in the field of drug delivery and pharmaceutical nanotechnology. Their ability to enhance bioavailability, protect labile drugs, provide sustained release, and enable targeted delivery has positioned them as a next-generation platform for therapeutic innovation. With continuous research focusing on improving synthesis efficiency, safety profiles, and targeted applications, nanosponges are poised to play a critical role in shaping future healthcare solutions. The

integration of nanosponge technology with other nanocarrier systems such as liposomes, dendrimers, and solid lipid nanoparticles could further enhance therapeutic performance and open new avenues for hybrid delivery systems. In conclusion, nanosponges stand as a remarkable innovation that bridges the gap between drug discovery and clinical efficacy. By addressing fundamental challenges of solubility, stability, and controlled release, they provide a robust solution for improving the bioavailability of a wide range of therapeutic agents. Continued research and collaboration between academia, industry, and regulatory bodies will be essential for translating this promising technology into market-ready formulations. As nanosponges continue to evolve, their role in personalized medicine, targeted therapy, and multidrug delivery is expected to expand, redefining the future landscape of drug delivery systems and patient-centered therapeutics[52].

CONCLUSION

The concept of nanosponge-based drug delivery has revolutionized modern pharmaceutics by offering a novel approach to address one of the most persistent challenges in drug formulation—poor bioavailability. The evolution of this technology reflects a deep understanding of nanoscience, polymer chemistry, and pharmaceutical engineering, converging into an adaptable platform capable of improving the solubility, stability, and targeted delivery of a wide range of therapeutic molecules. Over the last decade, nanosponges have emerged as an innovative solution to overcome limitations associated with traditional dosage forms, which often suffer from low dissolution rates, high variability in absorption, rapid metabolism, and suboptimal therapeutic efficacy. The continuous refinement in nanosponge synthesis, characterization, and functionalization has paved the way for highly efficient, biocompatible, and scalable systems that can enhance drug bioavailability and extend their clinical applications across diverse therapeutic domains. The versatility of nanosponges arises from their distinctive structural architecture—three-dimensional, porous, and nanoscale networks formed by crosslinked polymers capable of encapsulating hydrophobic as well as hydrophilic drugs. The dynamic internal cavities of these nanocarriers act as molecular sponges that can adsorb, entrap, and protect drugs against chemical degradation, hydrolysis, and photolytic breakdown. Once administered, the nanosponges gradually release the encapsulated drug at the target site, achieving sustained therapeutic action and minimizing side effects. This unique mechanism differentiates nanosponges from conventional nanocarriers such as liposomes or polymeric nanoparticles, which often

face limitations related to stability, leakage, or burst release. The ability of nanosponges to balance drug retention with controlled release kinetics has proven to be crucial for improving pharmacokinetic profiles and achieving better patient compliance. In recent years, a significant body of research has demonstrated that nanosponge formulations consistently outperform traditional drug delivery systems in terms of solubility enhancement, dissolution rate, and bioavailability. For drugs with inherently low aqueous solubility, such as curcumin, resveratrol, itraconazole, or paclitaxel, nanosponge encapsulation markedly increases their apparent solubility and facilitates better absorption through biological membranes. The nanoscale size of the particles ensures a higher surface area-to-volume ratio, allowing more intimate contact with the dissolution medium and biological interfaces. Additionally, the hydrophilic surface characteristics of polymeric nanosponges promote better dispersion in gastrointestinal fluids, which leads to improved oral absorption and systemic availability. These findings have been consistently supported by in vitro and in vivo studies demonstrating significant increases in plasma concentration, area under the curve (AUC), and prolonged half-life for nanosponge-based formulations compared to unmodified drug suspensions. Another noteworthy aspect of nanosponge innovation is its capability to achieve targeted and controlled drug delivery. Traditional oral and parenteral formulations often lead to fluctuations in plasma drug levels, which can cause either subtherapeutic effects or toxicity. Nanosponges, by contrast, ensure a more predictable and sustained drug release profile, maintaining drug concentrations within the therapeutic window for longer durations. Furthermore, functionalization of nanosponge surfaces with specific ligands such as antibodies, peptides, or folic acid has allowed the creation of actively targeted systems that recognize and bind to overexpressed receptors on diseased cells, particularly in oncology applications. This not only enhances local bioavailability at the pathological site but also reduces systemic exposure and side effects, marking a major advancement toward precision medicine. From a formulation perspective, the choice of polymer and crosslinking agent plays a decisive role in determining the performance of the nanosponge system. Cyclodextrin-based nanosponges remain the most extensively studied, owing to their natural biocompatibility and ability to form inclusion complexes with a wide variety of drugs. However, other materials such as ethyl cellulose, polyvinyl alcohol, and hyper-crosslinked resins have also been successfully employed to produce nanosponges with tailored properties. The degree of crosslinking controls the porosity, surface charge, and drug release behavior, enabling formulation scientists to fine-tune these parameters to

achieve desired therapeutic outcomes. The synthesis techniques—ranging from solvent evaporation, emulsion diffusion, and ultrasound-assisted methods to melt fusion and green synthesis—have evolved to yield reproducible nanosponge formulations with narrow particle size distribution and high drug entrapment efficiency. Advances in green chemistry have further contributed to making these processes more sustainable and environmentally friendly by minimizing the use of organic solvents and toxic reagents. Recent innovations have expanded the scope of nanosponge applications beyond conventional drug delivery. In transdermal and topical formulations, nanosponges provide enhanced skin retention and controlled release of active agents, minimizing irritation and improving patient compliance. In ophthalmic delivery, their ability to increase drug residence time on the ocular surface without compromising visual clarity represents a major breakthrough. Parenteral nanosponge formulations have shown improved circulation time and bioavailability for anticancer and anti-inflammatory drugs. Additionally, their use in nasal, pulmonary, and buccal delivery systems is being explored as a strategy for bypassing first-pass metabolism and achieving faster therapeutic onset. This adaptability makes nanosponges a universal platform that can be customized for different administration routes and therapeutic requirements. An emerging area of nanosponge research involves the development of stimuli-responsive systems capable of releasing drugs in response to specific environmental triggers such as pH, temperature, redox potential, or enzyme activity. These smart nanosponges allow site-specific and on-demand drug release, thereby maximizing therapeutic efficacy while minimizing off-target effects. For instance, pH-sensitive nanosponges have been designed for tumor-targeted drug delivery, exploiting the acidic microenvironment of cancer cells to trigger drug release. Similarly, enzyme-sensitive systems have been engineered to release antibiotics in response to bacterial enzyme secretion, enhancing antibacterial efficacy while preserving normal flora. These innovative designs represent a significant step forward in the evolution of nanosponge technology toward precision and personalized medicine. The role of nanosponges in improving bioavailability extends beyond small molecules to encompass macromolecules such as peptides, proteins, and nucleic acids. The encapsulation of fragile biomolecules within the protective nanosponge matrix prevents degradation and denaturation, allowing their controlled and sustained release. This approach has the potential to overcome major limitations in the delivery of biological therapeutics, which often face challenges of stability, rapid clearance, and immunogenicity. Furthermore, combining nanosponge systems with other nanocarriers, such as liposomes or

dendrimers, has resulted in hybrid systems that integrate the advantages of multiple technologies, leading to improved stability, targeting, and release performance. The widespread applicability of nanosponge technology across therapeutic fields underscores its importance in the future of drug delivery science. In oncology, nanosponge-based carriers have shown remarkable improvements in the bioavailability and cytotoxic potential of chemotherapeutic agents, enhancing tumor selectivity while minimizing systemic toxicity. In anti-inflammatory therapy, nanosponge systems have prolonged the release of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), providing sustained pain relief and reducing dosing frequency. Antimicrobial and antifungal nanosponges have improved local drug concentration and reduced resistance development by maintaining effective therapeutic levels over extended periods. In cardiovascular and neurological disorders, nanosponges facilitate the delivery of drugs across physiological barriers, such as the blood-brain barrier, improving the availability of therapeutic molecules in difficult-to-reach tissues. The potential of nanosponge formulations has also been explored in cosmeceutical and dermatological applications. By providing controlled release of vitamins, antioxidants, and skin-active ingredients, nanosponges enhance the efficacy and longevity of topical products. Their ability to reduce irritation, prevent degradation, and improve texture has made them attractive candidates in the formulation of advanced skincare and anti-aging products. In wound healing, nanosponge systems carrying anti-inflammatory or antimicrobial agents contribute to accelerated tissue regeneration and infection control. These examples highlight the broad spectrum of nanosponge applications beyond conventional pharmaceutical domains, demonstrating their role as a versatile and innovative platform technology. Despite these promising advancements, certain challenges remain that require attention to facilitate the full translation of nanosponge technology into commercial and clinical applications. Issues such as scalability of production, cost of materials, long-term stability, and regulatory approval pose barriers to industrial adoption. While laboratory-scale synthesis is well established, large-scale manufacturing requires optimization to maintain uniformity in particle size, drug loading, and crosslinking density. Standardization of characterization methods and development of quality control parameters are essential to ensure batch-to-batch consistency. Additionally, comprehensive toxicological evaluation is needed to confirm long-term biocompatibility, particularly for parenteral and implantable formulations. Regulatory authorities must establish clear guidelines specific to nanosponge systems to facilitate their approval and commercialization. Collaborative research efforts between

academia, pharmaceutical industries, and regulatory agencies are therefore critical to advancing this technology. Integration of computational modeling, machine learning, and artificial intelligence into nanosponge design and optimization can accelerate formulation development and predict in vivo behavior more accurately. These tools can aid in understanding structure–activity relationships, optimizing polymer–drug interactions, and predicting pharmacokinetic outcomes. Moreover, the incorporation of nanosponge formulations into patient-specific treatment strategies represents an exciting frontier in personalized medicine, where drug delivery can be tailored based on genetic, physiological, or pathological factors. Looking toward the future, the convergence of nanotechnology, biotechnology, and material science will likely expand the potential of nanosponge systems even further. Hybrid systems combining nanosponges with stimuli-responsive polymers, magnetic nanoparticles, or photothermal agents can create multifunctional platforms for targeted drug delivery, imaging, and therapy. The application of nanosponges in gene delivery, vaccine stabilization, and regenerative medicine is still in its infancy but holds immense promise. As global healthcare trends move toward patient-centric, minimally invasive, and precision-driven therapies, nanosponge technology stands as a key enabler capable of meeting these demands effectively. In essence, the journey of nanosponge development epitomizes scientific innovation directed toward improving human health and therapeutic efficacy. The consistent ability of nanosponges to enhance bioavailability, protect labile drugs, and deliver them in a controlled and targeted manner underscores their transformative potential in pharmaceutical research and clinical practice. While challenges related to regulatory acceptance and industrial scalability persist, the trajectory of ongoing research suggests that these obstacles will be gradually overcome through multidisciplinary innovation and technological advancement. Therefore, the future of drug delivery lies in the integration of intelligent, adaptive, and safe nanosystems capable of optimizing drug performance at every stage—from administration to absorption, distribution, and elimination. Nanosponges, with their robust design and broad applicability, represent one of the most promising candidates in this paradigm shift. Their continued development and refinement will undoubtedly contribute to the next generation of pharmaceutical formulations, transforming poorly soluble and unstable drugs into therapeutically effective and patient-friendly products. The concept of bioavailability enhancement through nanosponges thus embodies not just a technological advancement, but a scientific evolution that bridges the gap between molecular discovery and clinical realization, ensuring that effective therapies reach

patients in their most optimized form. advanced drug delivery strategies were expressed nanoparticle-based systems, hydrogels, and bio adhesive topical emulsions promising avenues to enhance TQ's bioavailability, stability site for specific action. In summary, TQ represents a multifunctional natural compound with exceptional potential to serve as a safe, effective, and sustainable therapeutic agent in modern wound management. Its capacity to modulate multiple molecular pathways, accelerate tissue regeneration, and prevent microbial infection positions it as a valuable candidate for future pharmacological innovation. Continued interdisciplinary research integrating nanotechnology, biomaterials, and clinical studies will be pivotal in establishing TQ as a cornerstone of next-generation wound healing therapeutics.

ACKNOWLEDGEMENT

I express my deepest sense of gratitude to Vinayaka Missions College of Pharmacy**,** Vinayaka Missions Research Foundation (Deemed to be University), Salem, Tamil Nadu, India, for providing me with the opportunity, facilities, and encouragement to carry out my research work entitled *"*Bioavailability enhancement through Nanosponges : Recent developments and applications*."*

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